Subacute sclerosing panencephalitis with atypical early features

Podostre stwardniające zapalenie mózgu z atypowymi wczesnymi objawami (SSPE)

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ABSTRACT

SSPE is a progressive, fatal neurological disorder of childhood and early adolescence, caused by a persistent measles virus infection of the brain. Due to atypical clinical presentation at onset, early SSPE diagnosis and clinical staging could be difficult and delayed. **Material and methods:** A group of 19 children (14 boys, 5 girls) with SSPE was diagnosed and treated at our Clinic from 1995 to 2008. Six children were non-immunized with no reliable data about measles vaccination in additional four children. Disease onset ranged from 4.5 to 16.8 years. Delay between onset and the SSPE diagnosis ranged from 1 month to 2.5 years (mean 4.7 months). **Results:** Cognitive deficits and/or behavior disorder followed by myoclonic jerks were recognized as initial, typical clinical picture in 42.1 %, while 57.9% of our patients had uncommon, initial clinical features. They presented focal motor deficits (2), seizures (4), hyperekplexia (1)], cortical blindness (2), optic disc swelling (1) and psychotic behavior (1). After 4 to 35 months (mean 14.2), since the disease onset, 15 of 19 children deceased. Patients with atypical SSPE onset showed significantly shorter period till death (mean 9.78 months) when compared to classical form (mean 20.83 months) ($p < 0.01$). First MRI disclosed no lesions in 5 patients. Neither myoclonus or Radermecker's EEG complexes were observed in a patient with initial hyperekplexia and drop attacks. **Conclusions:** Initial clinical manifestation of SSPE is highly variable. Later age of onset and atypical SSPE presentation could be an increasing differential problem leading to erroneous diagnosis of other neurological condition and subsequently to an inappropriate treatment.

Key words: subacute sclerosing panencephalitis, measles, atypical onset.

STRESZCZENIE

Wstęp i cel pracy: Podostre stwardniające zapalenie mózgu (SSPE) jest śmiertelną, postępującą chorobą układu nerwowego dzieci i młodzieży, spowodowaną przetrwałą infekcją wirusa odry wywołującym zapalenie mózgu. Z powodu nietypowych objawów w początkowym stadium, rozpoznanie choroby może być utrudnione i opóźnione. **Materiał i metody**: Grupa 19 dzieci (14 chłopców, 5 dziewcząt) z SSPE była diagnozowana i leczona w latach 1995-2008. Sześcioro dzieci było nieszczepionych przeciwko odrze, czworo dzieci nie posiadało rzetelnych danych dotyczących szczepienia. Objawy choroby wystąpiły między 4,4 a 16,8 rokiem życia. Opóźnienie pomiędzy wystąpieniem objawów a rozpoznaniem wynosiło od 1 miesiąca do 2,5 lat (średnia 4,7 miesięcy). **Wyniki:** Zaburzenia czynności poznawczych i/lub zaburzenia zachowania z ruchami mimowolnymy (mioklonie) były rozpoznane jako początkowe, typowe objawy kliniczne w 42,1%, podczas gdy 57,9% pacjentów miało nietypowe początkowe cechy kliniczne. Były to: zaburzenia ruchowe (2), napady padaczkowe (4), hyperekpleksja (1), ślepota korowa (2), obrzęk tarczy nerwu wzrokowego (1) i zaburzenia psychotyczne (1). Po upływie od 4 do 35 miesięcy (średnio 14,2) od wystąpienia choroby, 15 spośród 19 dzieci zmarło. U pacjentów z nietypowym obrazem klinicznym SSPE przebieg choroby był znacznie krótszy przed śmiercią (średnio 9,78 miesięcy) w porównaniu z typowym przebiegiem choroby (średnio 20,83 miesięcy) ($p<0.01$). Pierwsze badania neurobrazowe za pomocą rezonansu magnetycznego (MRI) nie wykazywały zmian u 5 pacjentów. Nie zaobserwowano mioklonii ani kompleksów Radermeckera w obrazie EEG u pacjentów z hyperekpleksją i napadami atonicznymi *(drop attacks)*. **Wnioski**: Pierwsze kliniczne objawy SSPE są bardzo zróżnicowane. Późniejsze wystąpienie i nietypowy początkowy obraz kliniczny SSPE prowadzą do błędnego rozpoznania innych schorzeń neurologicznych, i w konsekwencji, do nieprawidłowego leczenia.

Słowa kluczowe: podostre stwardniające zapalenie mózgu, odra, nietypowy początkowy obraz kliniczny.

SSPE is a rare, progressive, chronic, inflammatory and degenerative disease of the brain, representing slow viral infection caused by an aberrant measles virus. SSPE virus differs from wild-type measles viruses in the form of several mutations affecting the viral genome. Although its frequency is declined because of measles eradication, we still have endemic areas throughout the world, mainly in countries where effective vaccination programs have not been completely realized. In spite of widespread immunization, SSPE has recently reappeared also in developing countries.

The estimated annual incidence of SSPE in most of the developed world is $1/10^6$ population [1]. In the USA and Canada the incidence is $0.06/10^6$ with greater occurrence

in the southern American states [2]. Greater annual rate is seen in Eastern Europe, Middle East ($2.4/10^6$) and on the Indian subcontinent ($21/10^6$). This incidence increases to as high as 20-100 per 10^6 populations in underdeveloped countries where measles is still endemic because of indifferent vaccination compliance [3]. Fifty percent of patients who develop SSPE had measles before two years of age, and 75-80% before the age of four [4]. The incidence of SSPE among non-immunized children is 100-200 times higher than among those who have been immunized effectively.

Symptoms of SSPE vary widely among patients, depending on the stage of illness [2,5]. The initial symptoms of SSPE usually involve regression in cognitive functioning and behavior or recurrent myoclonic jerks. Parents and teachers may early notice difficulties in scholastic performance [4]. First stage is characterized by subtle behavioral changes, cognitive decline, emotional lability, irritability, lethargy and non-specific neurological symptoms typically followed by involuntary movements and myoclonic spasms. Natural history usually includes further mental deterioration, inability to walk, speech impairment, dysphagia, blindness and vegetative failure. In the final stage decerabrate and/or decorticate rigidity appear and the patient remain mute or comatose. The overall course of SSPE in the majority of patients lasts from 1 to 3 years. Up to 10% of cases show a fulminant or prolonged course [4]. Patients under the age of 4 often have a poor prognosis as a result of progressive or fulminant course. The disease is fatal in 90-95% of cases [6].

The guidelines of the International SSPE Consortium for the diagnosis and staging of SSPE [5] and Dyken's diagnostic criteria of SSPE [2] were widely used. These criteria include typical clinical (progressive cognitive decline with stereotyped myoclonic jerks), laboratory (elevated both cerebrospinal fluid globulin levels and measles antibody titers with oligoclonal CSF pattern), EEG pattern (generalized periodic Radermecker's complexes) or typical histological findings in brain biopsy/autopsy. Typical features such as myoclonus and periodic EEG complexes might be absent, or might be transient and undetected [7]. The low CSF measles antibody titer was reported in some atypical cases [8].

The EEG pattern is typical and very specific for SSPE, even when the clinical presentation is variable. The EEG abnormalities in SSPE were first described by Radermecker in 1949 [9]. The presence of high voltage (300-1000 μV) complexes, lasting 0.5-2 s and consisting of a 1-2 Hz slow wave preceded by a sharp wave is a characteristic pattern. These abnormalities are usually generalized, occurring with a periodicity of 4-16/min, synchronous with myoclonic jerks. In the early stage, these EEG abnormalities may be observed prior to any clinical manifestation. Since the classical description, cases with atypical features have been reported [10]. At present, there is no effective treatment. Oral isoprinosine and intrathecal or intraventricular alpha-interferon may prolong survival to some extent. Immunization against measles remains the most effective strategy against SSPE. The WHO has targeted the years 2005-2010 for global measles eradication.

Although SSPE is a rare disease, it has not disappeared entirely. The atypical initial presentation and unusual clinical features seem to be more often seen in the post-immunization decades. This could make significant diagnostic difficulties.

PATIENTS AND METHODS

Measles vaccination first became available in Serbia in 1971. A two-dose measles-mumps-rubella (MMR) vaccination strategy for children aged 12-15 months (first dose) and before the primary school entry at 5-7 years (second dose) was widely implemented since 1993. Second dose MMR was often administered in early adolescence (12 years) until 2006. Live measles vaccine is widely used.

The total number of habitants after the census of population in 1991 was 9,778,991 whereas in 2002 it was 7,498,001 and it was calculated without population of the province Kosovo and Metohija (Statistical Office of the Republic of Serbia). Following data published by Center for the Prevention and Control of Infectious Diseases and the Institute of Public Health of Serbia in Belgrade, incidence rates of measles are significantly decreased. In a period of 1994-1999 incidence (%000) was 3.28 – 7.20, with exception of 1997 when the measles outbreaks lead to the high incidence rate of 42.88. From 2000 to 2005 the incidence rates continued to decrease (0.36 – 2000; 0.24 – 2001; 0.36 – 2002; 0.20 – 2003; 0.11 – 2004 and 0.03 – 2005). Since 2000, no epidemiological data is available for the southern Serbian province of Kosovo and Metohija. There is no available Serbian register for the SSPE. Patients with SSPE we investigated were related to the single center study. So, the incidence rate of the disease in the country was not reachable to calculate.

All cases of SSPE diagnosed in our Clinic were collected since 1995. A group of 19 children (14 boys, 5 girls) with SSPE onset from 4.5 to 16.5 years (mean 11.05) was diagnosed and treated at our Clinic from 1995 to 2008. The following data was analyzed: initial clinical symptoms, interval between onset of revealing SSPE symptoms to diagnosis and initial neurophysiologic and neuroimaging findings.

Clinical staging scales were used to categorize patients, according to their clinical status into IA, IB, IIA, IIB, III and IV stages [11]. The guidelines of the International SSPE Consortium for the diagnosis and staging of SSPE and Dyken's diagnostic criteria of SSPE were adopted for the study [2,5]. These criteria included typical clinical, laboratory (serum and cerebrospinal fluid measles titer), EEG or histological features. The type of SSPE clinical progression was concluded following Dyken's criteria and it was described as fulminant, acute, subacute or chronic. Neurological condition was measured by the Neurological Disability Index (NDI) ranged from 0-100% [5]. According to the NDI values, four subgroups were formed: a) NDI= 80-100%; b) NDI= 50-80%; c) NDI = 30-50% and <30%. All cases fulfilling the diagnostic criteria of SSPE were analyzed. The medical records were critically reviewed.

Measles vaccination was given to 9 children, while 6 children were non-immunized. There was no reliable data about vaccination in four children. Disease onset ranged from 4.5 to 16.8 years (mean 10.25 in non-immunized and 9.83 in vaccinated patients) with no significant difference ($p<0.05$). Delay between onset of symptoms and the SSPE diagnosis ranged from 1 month to 2.5 years (mean 4.7 months).

Majority of cases (17 out of 19) fulfilled all diagnostic SSPE criteria. All patients presented typical progressive cognitive decline and neurological deterioration during the clinical course. Stereotyped myoclonic jerks developed in 17 out of 19 patients. Typical feature such as myoclonus was absent, time-limited (or might be transient therefore difficult to detected) in two patients. Generalized periodic Radermecker's EEG complexes were absent in both patients without myoclonus. All cases met the laboratory criteria (elevated both cerebrospinal fluid globulin levels and measles antibody titers with oligoclonal CSF pattern). Initial CT scans were done in IIA or IIB clinical stages in 6 patients while initial MRI examination was performed in IB or IIA stage of SSPE in 15 patients.

Parents or caregivers gave written informed consent for children to participate in the study. The Ethics Committee of our University Clinic and the Institutional Review Board of Faculy of Medicine, University of Belgrade approved the study.

Descriptive statistics included means, standard deviations and standard errors of scores achieved. The results were analyzed by the Student's *t*-test for paired observations to determine the significance of differences for means between independent groups.

RESULTS

The mean SSPE onset in our 19 patients was 10.05 years, SD 3.34. Delay between the onset of symptoms and the diagnosis of SSPE ranged from one month to 2.5 years. Six children were non-immunized against measles. Complete vaccination was performed in 8 patients, and they received two doses of measles vaccine at 1 and 6-7 years. First dose was administered in 9 month and repeated in his 16 months in one additional case (patient No. 7, Table I). There was no available medical data to confirm the immunization in four children. Eight children had a history of documented measles infection, and they were either not vaccinated against measles (5) or the data on immunization was not available (two). In remaining case, already cited (patient No. 7) immunization against measles was performed in 9th month of life despite probable measles infection which occurred two months earlier. Out of these cases, three had measles at the age of less than one year and 5 were infected at 2 to 5 years of age. Four children were infected during the measles outbreaks. The mean interval between documented measles infection and onset of SSPE was 5.4 years (range 4 - 7.5).

Learning difficulties of various severities and/or behavior disorder followed by myoclonic jerks were recognized as initial, typical clinical picture in 8 (42.1 %) while more than half (11; 57.9%) of our patients initially presented uncommon clinical features. They presented focal motor deficits (2), seizures (4), hyperekplexia (1), cortical blindness (2), optic disc swelling (1) and psychotic behavior (1). Periodical myoclonic jerks followed first clinical finding for 15 days to 6 months with exception of patients No 4 and 19 (Table I).

Table I. Demographic and some clinical characteristics of studied SSPE patients

No	Sex	Vaccination	Age at onset	Initial clinical sign of SSPE	Disease duration (mo)
1	M	Yes	6	Cognitive dysfunction	> 60
2	M	Yes	7.5	Behavioral disorder and cognitive decline	> 24
3	M	Yes	13	Learning disability	35
4	M	No	!4.5	Hyperekplexia and drop attacks	> 24
5	M	NK	8	Left-sided spastic hemiparesis	22
6	F	Yes	!2	Behavioral disorder and cognitive decline	18
7	M	Yes	4.5	Cognitive dysfunction	14
8	M	Yes	9	Segmental myoclonus and learning difficulties	26
9	F	Yes	8.5	Focal motor seizures	> 24
10	M	NK	13.5	Behavioral disorder and cognitive decline	14
11	M	No	7.5	Atypical absence seizures	12
12	F	No	13	Cortical blindness	11
13	M	NK	9	Left-sided spastic hemiparesis	10
14	M	Yes	11.5	Complex partial epilepsy	10
15	F	No	8	Optic disc swallowing	6
16	M	Yes	16.5	Visual loss	8
17	M	NK	14	Psychotic behavior	5
18	M	No	6.5	Secondary generalized focal motor seizure	4
19	F	No	8.5	Hyperactive behavior, cognitive decline	18

M-male F-female

Initial visual symptoms revealed the disease before typical cognitive deterioration and myoclonus in three patients, with cortical blindness in two children aged 13 and 16.5 years and with optic disc swallowing in an 8-year old girl. Two to five months later, cognitive decline with altered behavior occurred. Periodic myoclonic jerks began one to six month after the visual symptoms. The diagnosis was made after the onset of myoclonus. The patients died 6 to 11 months after the loss of vision.

Intractable seizures in four patients aged from 6.5 to 11.5 years (mean 8.6 years) preceded cognitive and behavioral decline for 6 months to 1.5 years. Pharmacoresistant focal motor seizures with secondary generalization in two, complex partial seizures in one and atypical absences in remaining child occurred as initial SSPE presentation. Focal spike-slow waves over temporal (2) or frontal-parietal (1) regions and/or bilateral spike-wave discharges correlated with seizure type before the appearance of SSPE typical EEG abnormalities. Therapeutic response to initial carbamazepine in 15 to 25 mg/kg/day (3) for focal seizures was poor. Therapy with valproate (30-45 mg/kg/day) or topiramate (5-12 mg/kg/day) alone or with adjunctive benzodiazepines (clonazepam, clobazam, lorazepam) resulted in better, but non-complete seizure control. Absence seizures were completely controlled by valproate (35 mg/kg/day), but generalized tonic-clonic seizures (1-3 monthly) occurred in a same patient and were unresponsive to valproate, phenobarbital or levetiracetam.

Moderate left-sided spastic hemiparesis was diagnosed in two children, 1.5 and 4 months before the onset of learning difficulties and segmental myoclonus. In one 8 year-old boy it was transitory and short-term (10 days), while in a 9-year old boy no fluctuation in its severity and extent was observed (patients No 5 and 13). Hyperekplexia developed in a 14.5 year-old boy, and it was soon followed by drop attacks (patient No 4, Table I).

Psychotic behavior with hallucination, autistic features, lack of emotional resonance and delusions was SSPE revealing condition in one 14 year-old adolescent. Two weeks later he demonstrated brief, multi-segmental myoclonia accompanied with EEG abnormalities characteristic for the stage II of SSPE. His speech became ineligible. Two months after the onset, he was bedridden, speechless and in severe neurological condition with sub-continuous myoclonic jerks. During this acute course, he had dementia, decorticate state and rigidity and he died after 5 months of disease duration.

Distribution of the type of SSPE progression, following Dyken's criteria (1985) was summarized in Table II. NDI was mainly high: 80-100% in 6, 50-80% -8, 30-50%-3 and <30% in two patients only. Chronic course was observed in two patients with atypical onset (hyperekplexia, focal motor seizures) and in 4 patients with typical SSPE (Table I).

Six non-vaccinated children had the mean age of SSPE onset ranged from 6.5 to 14.5 years (mean 9.67; SD 3.2). Two of them presented early visual loss, two had seizures while remaining patients had cognitive dysfunction (1) and hyperekplexia (1) as initial clinical sign. Clinical course was fulminant in one, acute in one, subacute in two and chronic in remaining two patients (Tables I and II). All but one (patient No 4) died from 4 to 18 months after the disease onset. Their NDI was > 50 % in all cases. A 6.5 year-old boy with initial seizures and normal MRI presented fulminant course of SSPE.

After 4 to 35 months (mean 14.2, SD 8.48), since the disease onset, 15 of 19 children deceased. Analysis of the prognosis showed the significant relationship between type of SSPE onset and the disease duration. Subgroup of 9/11 patients with atypical SSPE onset showed significantly shorter period till death (mean 9.78 ± 5.36 months) when compared to a subgroup of 6/8 patients with classical form (mean 20.83 ± 8.2 months) (T- 3.18, DF 13, CI 99.27 %, $p < 0.01$).

Initial CT scans, performed in IIA or IIB clinical stages in 6 patients showed normal result in one patient, moderate cortical atrophy in 4, and/or localized hypodense area in the left occipital region in a 13 year-old girl with cortical

Table II. Clinical course of 19 SSPE patients

Parameter	No of patients			%
	A	B	Total (A+B)	
Type of SSPE progression				
Fulminant	-	1	1	05.2
Acute	1	2	3	15.8
Subacute	3	6	9	47.4
Chronic	5	1	6	31.6
Total	9	10	19	100.0
Neurological disability index				
80-100%	2	4	6	31.6
50-80%	3	5	8	42.1
30-50%	2	1	3	15.8
<30%	2		2	10.5
Total	9	10	19	100.0

A-vaccinated, B-non-vaccinated + with unknown data on immunization

Table III. Initial neuroimaging (CT and MRI) findings in 19 SSPE patients

Patient (No)	Initial CT	Initial MRI
1	normal	bilateral and diffuse lesions of periventricular and subcortical white matter
2	mild parietal cortical atrophy	ND
3	moderate cortical atrophy	multiple lesions of periventricular and subcortical white matter
4	ND	normal
5	ND	bilateral and diffuse abnormal T2 increased signal in the periventricular and subcortical white matter
6	ND	bilateral and diffuse lesions in the periventricular and subcortical white matter
7	ND	bilateral lesions of basal ganglia
8	ND	normal
9	ND	bilateral lesions in the periventricular and subcortical white matter
10	ND	ND
11	ND	normal
12	localized hypodense area in the occipital regions	ND
13	ND	focal parenchymatous changes in right frontal lobe
14	moderate cortical atrophy	ND
15	ND	focal parenchymatous lesions in parietal-occipital regions
16	ND	normal
17	ND	normal
18	ND	localized demyelinative lesion in the brain stem
19	moderate cortical atrophy	multiple bilateral lesions and atrophy of periventricular and subcortical white matter

CT- computerized tomography; MRI magnetic resonance imaging; ND not done

blindness as initial SSPE symptom (patient No 12, Tables I and III). Neuromaging -MRI studies in early IB or IIA clinical stages of SSPE were performed in 15 patients. First MRI disclosed no lesions in 5 patients. Bilateral and diffuse abnormal T2 increased signal in the periventricular and subcortical white matter was revealed in 6 cases. Focal parenchymatous changes were seen in two children. Lesions localized either in the basal ganglia or in the brain stem were disclosed in two remaining patients. Irrespective of normal MRI of the brain, performed in a stage I, patient No 17 with acute SSPE died 5 months after the disease onset, while patient No 16 with subacute SSPE and normal MRI died 8 month after the initial symptoms. No MRI control was done. No MRI was done in 4 patients including one patient (No 10) without any neuroimaging study. No consistent association was found between focal seizures or lateralizing neurological deficits and imaging findings.

In a 16.5 year-old patients (No 16) with initial visual loss, typical EEG abnormalities nearly preceded the gradual visual acuity reduction, and were recorded for one month before appearance of myoclonic jerks. Repeated EEGs of a patient No 19 showed the paroxysmal lateralized epileptiform discharges, but without SSPE pathognomonic complexes. She presented with rare non-periodic myoclonus atypically involved in a clinical framework of the disease. Both myoclonus and Radermecker's complexes were not observed in a patient No 4 with hyperekplexia and drop attacks as initial SSPE manifestation. Both patients (No 4 and 19) were classified as having chronic SSPE, lasting for 18 and >24 months.

Inosiplex (isoprinosin) (100 mg/kg/day) was administered in 13 patients after the diagnosis was made. In four patients it was given together with interpherone-alpha2b (100 000 U/m^2). Antiepileptic drugs were applied in all cases. In addition, high doses of i.v.IGg were administered in two patients. Efficacy and safety of the therapy will be separately analyzed.

DISCUSSION

There is no available registry on SSPE in Serbian population. Epidemiological data are very difficult to interpret for last two decades because of numerous political and demographic changes and events. Universal immunization against measles begun in Serbia in 1971, while combined MMR was

available since 1993. The measles immunization in Serbia is compulsory, but often without rigorously pursued vaccination in previous practice. The first dose is recommended at 12-15 months of age. With infection that occurred early in life and the poor compliance with reporting measles infection in some cases, the later vaccine could be non-protective. Direct comparison between countries is difficult because different epidemiological parameters were used and these studies were conducted at different time periods.

The onset of SSPE follows a latent period of 5 to 15 years after the measles infection [1,12,-14]. The age of the first presentation ranged from 4.5 to 16.5 years (mean 10.05; SD 3.33) in our study. Factors affecting the duration of the latent period are unknown. In an epidemiological study relating the period from 1952 to 1983, the mean latent period was reported as 5.5 years, while the average age of onset was 7.7 years in 194 children with SSPE in former Yugoslavia [15].

In a group of 36 patients from Turkey, Ozturk et al. [12] reported the mean age of onset at 13.1 years (range 4 to 23). Anlar et al. [16] reported the recent decline of the latent period from 9.9 to 5.9 years in the same country. They suggested that epidemiological pattern of SSPE was affected by changes of immunization practice in Turkey and by the epidemiology of measles. The mean age of onset was 9.8 years in a pre-immunization period, to be dramatically reduced to 7.6 years of age with developed immunization.

The SSPE now appears to have altered epidemiological and clinical expression [16,17]. Both measles and SSPE declined significantly after measles immunization, with the mean age of SSPE onset increasing from <10 years to approximately 14 years [3,5]. With measles immunization, the incidence rate of measles also dramatically decreased in Serbia, and it was 0.03 in 2005. During the period 1995-2002, 40 SSPE cases, mainly non-immunized were diagnosed in Bulgaria. Children had earlier measles infection (average 11 months) and earlier onset of SSPE (mean 8.4 years) than previously reported [18].

The mean SSPE onset in our 19 patients was 10.05 years, SD 3.34. The difference in age of SSPE onset in our patients is non-significant and might be related to the immunization with mean 10.25, SD 3.1 years in non-immunized and 9.83, SD 3.75 years in vaccinated patients ($p<0.05$). When compared to data from Yugoslav study, the mean age of onset was 7.7 years in a period from 1952 to 1983 (including pre-immunization era till 1971) [15], to be increased to 10.05 years of age with developed immunization (1995 to 2008). This comparison is not quite adequate because our data was provided from Serbia only and as a single center study.

SSPE has been also reported in some patients with a history of measles vaccination. Manayani et al.[3] reported 24% cases of SSPE with a history of measles vaccination and 36% of patients with no symptomatic measles infection. The disease in vaccinated children is thought to result from a subclinical or unrecognized measles infection that occurred before the immunization (mainly administered at 12-15 months of age). It could be also attributable to the wild type of measles virus. There is no evidence to suggest that attenuated vaccine virus is responsible for sporadic cases of SSPE [4]. Barrero et al. [19] reported eight children who had measles as infants during the 1998 measles outbreak in Argentina and in whom SSPE developed 4 years later. Phylogenetic analysis of three SSPE cases showed that these children were infected with wild-type circulating D6 virus before immunization. They received measles vaccine according to the schedule, but vaccinal strains were not detected in brain tissue. In 8 out of 19 our patients the history of complete measles vaccination was reported. We also presume that subclinical or unrecognized measles infection prior to immunization or poor seroconversion, vaccine failure (faulty storage, improper cold chain) were associated with SSPE in some of our patients. Detection of the wild-type viruses was not carried out.

The majority of patients with SSPE exhibit subacute neurological deterioration, which usually proceeds from cognitive decline, behavioral disorder, myoclonus, seizures and dementia till death [2,5]. The diagnosis is easy made when typical clinical and EEG features appear, but it is difficult during the early stage when such signs are minimal or absent [20]. Among 307 patients evaluated, initial diagnosis was other than SSPE in 78.8%. These included seizures, metachromatic leukodystrophy, cerebral palsy, hemiparkinsonism, Wilson's disease, nutritional amblyopia, malingering and others [6]. As SSPE is a rare disease and the clinical diagnosis can be mistaken for other neurodegenerative disorders, the definitive diagnosis is often delayed, and made in later stages of the disease. So, the time between first symptoms and diagnosis varied from one day to 13 years [6,13]. It ranged from 1 month to 2.5 years (mean 4.7 months) in our group of patients. In addition, mild behavioral disturbances that can be seen in stage IA often did not attract attention to the general physician [13]. In a 25-year epidemiological study in Bulgaria, Bojinova et al. found 9 out of 40 cases (22.5%) presented with atypical features and two (5%) were previously immunized [18].

Three patients in our group presented initial visual symptoms. Cortical blindness in two and papillary edema in one patient were observed before the typical cognitive deterioration and myoclonus. Ocular and visual manifestations (cortical blindness, chorioretinitis, optic atrophy, macular retinitis) are usually concurrent with cognitive decline, but they may precede neurological SSPE manifestations by several weeks/months [1,4,21]. Cortical blindness revealing SSPE is rare [22-24]. Right occipital hypodense zone in our patient No 12 was seen on CT scans as in the case of a patient initially presented with cortical blindness and rapidly progressing encephalopathy within 15 days [23]. In a 4-year old boy with acute vision loss resulting from cortical blindness, typical SSPE findings developed 7 months after the onset of vision loss [24]. Our cases presented with cognitive decline for 2 to 5 months and with myoclonus for one to 6 months after the onset of visual symptoms. The patient No 15 – an 8 year-old girl presented with unilateral optic disc swallowing before acute progression of typical SSPE symptoms. Our patients with initial visual symptoms (No 12, 15, 16) died 11, 6 and 8 months after their

onset (Table 1). Macular swelling and visual impairment in patients with rapid deterioration raised the possibility of measles virus-acquired virulent neurotropism in the retina before invading the brain [4,17,21,24]. The macular findings could be mistaken for a heredodegenerative disorder and the diagnosis of SSPE was postponed until typical findings took place. Although in the early stages lesions usually involve parietal-occipital cortical-subcortical regions asymmetrically, as in our patients, there is no strong correlation between MRI findings and clinical stage in SSPE [25].

SSPE presenting focal or unilateral neurological signs (hemiparesis, extrapyramidal hyperkinesias, unilateral involuntary movements etc.) was also reported [11]. Some children were initially thought to have acute disseminated encephalomyelitis following neurological deficits (mainly hemiparesis and ataxia) and MRI scattered areas of T2 and hyperintensities in the white matter [26]. Early gait disturbances were observed in 5 out 48 Brazilian SSPE patients [13]. In a case of fulminant SSPE with hemiparesis, MRI showed frontal and parieto-occipital demyelination extended to nuclear areas [27]. Initial neurological deficits could be accompanied by headache, seizures, nausea and vomiting [12]. In two our patients (No 5, No 13, Table I), boys aged 8 and 9, an acute left-sided spastic hemiparesis preceded cognitive decline and myoclonus. First MRI (4 and 5 months after the disease onset) revealed bilateral lesions in the periventricular and subcortical white matter (patient No 5) and focal parenchymatous changes in right frontal lobe (patient No 13, Table I).

Kissani et al. [28] reported seizures revealing SSPE in 10% of 70 Moroccan cases. In the majority of cases (6 of 7) seizures were classified as intractable focal with or without secondary generalization suggesting a focalized encephalitis process. Conversely, seizures that occurred later were in most cases of generalized tonic-clonic seizure (GTCS) type. In a group of 48 Brazilian patients, 11 started with GTCS as initial manifestation [13]. In a large study conducted in India [6] 6.2% SSPE patients presented initial seizures. Seizures as initial event occurred in 4(21.05%) of our patients. As reported in the Moroccan study, in all but one case, intractable focal motor or complex seizures preceded the typical SSPE course. Differently from Brazilian group, there were no patients with primary GTCS revealing SSPE. Initial infantile spasms, atonic spells or atypical absences were unusual. Kubota at al. reported a case of 2-year old girl with first seizure occurred 9 months after measles infection. At 9.5 years of age she presented second, complex focal seizure and right hemiconvulsions. Her MRI was normal, seizures were controlled by valproate, but EEG showed diffuse periodic synchronous discharges. At 12 years of age she presented progressive mental regression and further diagnosed as stage I of SSPE. Second seizure, associated with EEG abnormalities, could be considered as initial SSPE event [20].

Rare cases of SSPE initially with psychotic, schizophrenic, paranoid-hallucinatory behavior or psychosis were reported [29]. A case of non-vaccinated 13-year old boy with initial emotional lability and major depression, soon followed by brutal neurological, cognitive decline and myoclonus was reported [30]. Our patient (No 17) a 14 year-old boy presented psychotic behavior, rapidly deteriorated and deceased after 5 months of severe clinical condition.

Chung et al. [7] reported a case of rapidly progressive SSPE presented as transient visual agnosia and myoclonus in a 14-year-old male. Two months later he developed intractable seizures. There were no typical periodic complexes in serial EEG monitoring and CSF measles antibody titer was negative. MRI study revealed bilateral T2-weighted hyperintensity, including both hippocampi being involved. The diagnosis was made by molecular and histological examination of open brain biopsy tissue. He succumbed two months after initial presentation. An unusual case of fulminant SSPE in an 18-year old man from India with a course of 19 days only, with hemiparesis in absence of myoclonus and cognitive decline, was reported. Both CSF protein and cell count were normal. An autopsy study disclosed the genotype D7 of measles [27]. Normal CT/MRI findings were found in 1/3 out of 58 patients investigated by Praven-kumar et al. [14].

Atypical EEGs were noted in 21 out of 58 cases in one Indian setting [14]. Unspecific initial or early EEG changes in SSPE could make diagnostic difficulties. Atypical EEG abnormalities were also reported in some cases with SSPE: no pathognomonic complexes, unilateral or abortive complexes, resembling paroxysmal lateralized epileptiform discharges, isolated non-periodic transients, periodic lateralized epileptiform discharges, non-convulsive status epilepticus, focal slowing and spikes before the clinical presentation etc.[10,11,14]. Atypical EEG patterns are more frequent in later SSPE stages and with longer disease duration. The EEG changes could precede clinical symptoms in patients with SSPE. In 4/10 SSPE patients with hemiplegia, EEG discharges were ipsilateral with neurological deficit [14] as in one of our two patients. Repeated EEGs of patient No 19 showed the paroxysmal lateralized epileptiform discharges but without SSPE pathognomonic complexes. Both myoclonus and Radermecker`s complexes were not observed in a patient No 4 with hyperekplexia and drop attacks as initial SSPE manifestation.

CONCLUSION

SSPE is a rare neurodegenerative disorder caused by persistent measles infection in the brain. A group of 19 children with SSPE was diagnosed and treated at our Clinic from 1995 to 2008. Initial clinical manifestation of SSPE is highly variable. Cognitive deficits and/or behavior disorder and myoclonic jerks were recognized as initial, typical clinical picture in 42.1 %, while 57.9% of patients had uncommon early clinical features. They presented focal motor deficits, seizures, hyperekplexia, cortical blindness, optic disc swelling and psychotic behavior. Atypical SSPE onset was significantly associated with shorter period till death when compared to classical form ($p < 0.01$). First MRI disclosed no lesions in 5 patients. Due to uncommon clinical presentation at onset, early SSPE diagnosis could be difficult and delayed.

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